C. R. Acad. Sci. Paris, Sciences de la vie/Life sciences, 1993; 316 : 1150-7

Cytokines and the function of the mature nervous system

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ABSTRACT

In addition to the role that cytokines (growth factors, interleukins, instructive factors) play in regulating neuronal survival, growth and gene expression during development, recent evidence suggests that these intercellular signals can also control similar functions in the normal, as well as the injured, adult nervous system. Some of this evidence is summarized here, with particular emphasis on the potential role of cytokines in synaptic function and plasticity. ▲

Key words : NGF, LIF, TGF, PDGF, IGF, FGF, TNF.

It is generally accepted that cytokines, acting both as permissive growth factors and as instructive differentiation factors, can regulate the differentiation and function of synapses. It may not be as widely appreciated that the mechanisms and molecules regulating the development of circuits in the embryonic nervous system can also influence the flow of synaptic information in maturity. This is very likely done by modifying the efficacy of transmission at established connections, and it may also be accomplished by regulating the rearrangement of such connections. Proteins and steroids can act retrogradely as trophic factors, controlling the number of neurons that innervate a target cell. There is also evidence that these factors can act anterogradely, allowing a neuron to influence its targets in ways that are not yet fully understood. Moreover, there is evidence that neurotrophic factors can be produced by glial and immune cells, as well as by the neuron itself, acting in an autocrine fashion. In addition, cytokines can act instructively, to direct neurons to adopt one or another phenotype. Dramatic changes in transmitter and associated neuropeptide systems are known to occur during normal development, and are likely caused by the ability of instructive neuronal differentiation factors to direct gene expression.

These phenomena of plasticity in growth and gene expression persist into maturity. I review here some of the evidence implicating growth and differentiation factors in synaptic plasticity and particular behaviors in the normal, adult organism. These findings contribute to the growing realization that the adult system is meta-stable, representing a balance between growth and withdrawal, gene induction and repression. The evidence also supports the idea that cytokines are required for maintenance of the mature system, and that these proteins and hormones could, therefore, be used for therapeutic intervention. While cytokines are already being tested for their capacity to rescue dying neurons in human neurodegenerative diseases, they may also be useful for changing the balance of transmitter and neuropeptide systems, and even connectivity, with the goal of modifying behavioral abnormalities.

Trophic and differentiation factors in development

Many cytokine families, protein and steroid, possess neurotrophic activity, supporting survival and growth. The nerve growth factor (NGF) neurotrophin family is now composed of at least four members : NGF, brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and NT-4/5 [1, 2]. Another emerging family is the neuropoietic cytokine group, so named for their prominent overlapping activities on neural and hematopoietic cells. This family currently includes the cholinergic neuronal differentiation factor (CDF; also known as leukemia inhibitory factor, LIF), ciliary neurotrophic factor (CNTF), oncostatin M (OSM), growth promoting factor (GPA), and interleukins 6 and 11 (IL-6, 11) [3-5]. Other cytokines with trophic activity for various neuronal populations include the insulin-like growth factors (IGFs [6, 7]), fibroblast growth factors (FGFs [8-10]), platelet-derived growth factors (PDGFs [11-13]), and members of the transforming growth factor superfamily (TGFs [14-16]). Gonadal as well as corticosteroids and ecdysteroids also regulate neuronal survival and growth [17-20].

It is striking that trophic factors, even those within a single family, can act on partially overlapping populations of neurons [21]. While responsivity to the various family members is determined by which neurotrophin or neuropoietic cytokine receptor, for instance, is expressed on a neuron's surface, these receptors often do not display absolute specificity for the various members of the family [22-26]. The meaning of this phenomenon for development is not yet clear. Another emerging generalization is that many or all of the trophic proteins can be produced by neurons as well as glia, peripheral tissues and immune cells [27]. Moreover, steroids can be produced by peripheral tissues as well as the nervous system [28, 29]. These findings indicate that trophic factors may function in modes other than as traditional, target-derived, retrograde agents.

An anterograde action for trophic factors is suggested by findings with bFGF in the visual system. This protein is

synthesized and released by retinal cells *in vivo* [30], and it can be anterogradely transported by retinal ganglion neurons to their target sites in the lateral geniculate body and the superior colliculus [31]. There is also evidence that the neurotransmitter vesicles of adrenal chromaffin cells may contain bFGF [32, 33]. Moreover, preliminary reports indicate that neurotrophic activity is released from these cells when they are depolarized [34, 35]. Chromaffin cells also contain several TGF-βs and a CNTF-like trophic factor [35]. Since chromaffin cells resemble neurons in many respects, and neurons themselves produce neurotrophic factors [36-38], it seems highly likely that these factors are used in the nervous system in both the antero- and retrograde directions. There is ample evidence that anterograde influences can regulate neuronal survival and gene expression during development [39, 40]. It is also worth noting that nonneuronal target tissues express receptors for neurotrophic factors [38, 41].

The finding that a neuron can express receptors for a factor that it produces suggests an autocrine or even an intracrine role. In fact, sensory, sympathetic, motor and hippocampal pyramidal neurons express cognate trophic factor and receptor mRNAs [21]. Glia have long been thought to provide support for neurons, and the localization of trophic factor mRNAs to such cells has bolstered this view [42, 43]. It should be pointed out, however, that the predominant site of expression for several trophic factors in the intact brain is in neurons [36, 44-47]. The role of immune cells in the trophic context will be considered below.

In addition to supporting the survival and growth of neurons, many of these factors have been shown to regulate the expression of specific sets of neuronal genes during differentiation. The genes for neurotransmitters and neuropeptides allow a particular neuron to be recognized by this set of phenotypic markers. The neuropoietic cytokines have been intensively studied in this regard, particularly with sympathetic neurons as the target cell [5, 27, 48]. In addition, activin A, a member of the TGF superfamily, induces a different, but partially overlapping set of genes when compared to the neuropoietic cytokines in the cultured sympathetic neuron assay [48]. Activin A can also mimic a target-derived factor that induces expression of the neuropeptide somatostatin (SOM) in cultured ciliary ganglion neurons [49]. Moreover, activin A mRNA is found in cells cultured from this target (the choroid [49]). In addition, BDNF can selectively induce the expression of the neuropeptides SOM and neuropeptide Y (NPY) in cultures of rat cortical neurons, without affecting neuronal survival in this population [50]. Similarly, NGF can selectively induce the expression of particular neuropeptides in sensory neurons [51].

Growth and differentiation factors in the adult nervous system

Growth and differentiation factors are active in the normal, undamaged, adult nervous system, and they are involved in the response to injury as well. It is clear that the adult nervous system exists in a state of dynamic equilibrium [52]. Denervation of adult skeletal muscle or blocking activity induced by the nerve, for example, causes a series of changes in the myotubes that can be viewed as a return to an embryonic, preinnervation state. When nerves subsequently reinnervate the myotubes, a sequence of changes that were seen in development unfolds once again, producing a mature muscle. Thus, the state of differentiation of the muscle is plastic, and depends on its innervation [52, 53].

Similar plastic phenomena are observed in the nerve fibers themselves when imbalances are introduced experimentally [52, 53]. In partially denervated muscles, the remaining, intact axons sprout and innervate the denervated myotubes. An activity-based mechanism can be invoked here as well, because sprouting can also be induced by blocking nerve-muscle transmission or paralyzing the muscle, and electrical stimulation of the muscle prevents sprouting induced by partial denervation. These and other results illustrate that the mature nerve-muscle system is in a state of dynamic balance. Similar phenomena have been observed in neuron-neuron synapses. Intact, undisturbed neuron-neuron and neuron-muscle junctions in the adult mammal display continual sprouting of small axonal and dendritic branches, parts of postsynaptic gutters are vacated, and new synaptic contacts are formed [54, 55].

Sprouting from intact synapses can be evoked in the adult by administration of trophic factors such as IGF-2 and CNTF [56, 57]. NGF continues to be synthesized in adult peripheral tissues and retrogradely transported by mature sensory neurons [58-60]. In addition, injection of antibodies to trophic factors into adult animals can induce regressive changes in sensitive neuronal populations [61-64], and NGF administration to adult rats affects the physiological properties of nociceptive sensory neurons [65]. Injection of NGF into brains of aged rats can improve spatial memory, without affecting the number of NGF-receptor-positive neurons in the nucleus basalis [66]. Qualitative as well as quantitative aspects of neuronal gene expression are also in a state of flux in maturity. Continued presence of neuropoietic and neurotrophic factors is required for maintenance of neuropeptide expression by cultured peripheral and central nervous system (CNS) neurons [67]. Rerouting of axons to novel targets in the adult rat can alter neuropeptide phenotype as well [68]. Conversely, perturbation of normal neuronal activity can regulate neurotrophic factor expression. For example, blockade of nicotinic, cholinergic activity can up-regulate BDNF and NGF mRNA in the adult hippocampus [69]. In addition, the balance between the activity of the glutaminergic and γ-aminobutyric acid systems can regulate the level of BDNF and NGF mRNA in this structure [70]. In the visual system, physiological variations in sensory stimulation can induce dramatic changes in BDNF expression in adult rat visual cortex [71]. Light-evoked activity can control the growth and sprouting of axons in the visual cortex, and administration of NGF can prevent the shift in ocular dominance normally observed in monocularly-deprived rats and cats [72].

Neuropoietic cytokines may also be involved in the regulation of these phenomena. For instance, CDF/LIF and its receptor mRNA levels are highest in the visual cortex and hippocampus, reaching maximal values in adulthood [73-76]. Moreover, mice in which the CDF/LIF gene has been disrupted by homologous recombination

display severe alterations in neuronal organization and phenotypes in the hippocampus and visual cortex [77]. It is not yet known, however, whether these alterations occur during development or in maturity. It is clear that the adult sensory cortex is capable of enormous plasticity, displaying major changes in sensory maps very quickly [78]. It will be of great interest to see what role trophic and differentiation factors play in these remarkable changes.

Steroids are another key group of trophic and differentiation factors active in the CNS. In addition to their organizational effects on the embryonic brain [19], gonadal steroids can regulate neuropeptide expression in the adult CNS independently of effects on neuronal survival and growth. Estrogen controls the differential expression of cholecystokinin (CCK) and substance P (SP) mRNAs in a sexually dimorphic pathway in the amygdala [79-80]. The instructive nature of this regulation is particularly striking because these two neuropeptides are co-expressed in the same neurons. The physiological nature of this action is evidenced by the variation in the number of CCK-positive neurons during the estrous cycle [81]. The variation in CCK content makes it likely that the character of the synaptic transmission between this subset of estrogen-sensitive neurons in the amygdala and their target cells in the preoptic area is altered during the estrous cycle. Such alterations have been termed "chemical switching" of transmission by these cells [82, 83]. Another striking example of this phenomenon is the differential regulation of galanin (GAL) and lutenizing hormone releasing hormone (LHRH) in neurons that express both neuropeptides simultaneously [84]. In addition, estradiol can alter neuronal circuitry very rapidly. In the 24 h period between proestrous and estrous, for example, synaptic density in the CA1 region of the hippocampus declines about a third [85], a result consistent with changes in synaptic density evoked by experimental manipulations in hormone levels [86].

In the paraventricular nucleus of the hypothalamus, glucocorticoid hormone exerts a selective, negative feedback on the expression of corticotropin-releasing factor (CRF) and vasopressin (VP), without affecting levels of enkephalin and neurotensin [83]. CRF mRNA levels follow the diurnal surge in corticosterone, and adrenalectomy results in higher CRF and a massive increase in VP [87, 88]. Independent control of the 8 different neuropeptides in these neurons may reflect the fact that these neurons are thought to form various synapses with different functions as their axons traverse the hypothalamus, median eminence and anterior pituitary [83]. The three physiological conditions of chronically low, medium and high circulating corticosterone would yield paraventricular neurons of three distinct chemical states. This steroid, in its neuronal differentiation factor role, could thus alter synaptic function in an anatomically stable circuit that is the final common pathway for mediating the pituitary-adrenal response to stress, on a minute-to-minute time scale [88].

Glucocorticoids may also act indirectly to alter neuronal gene expression. For example, corticosterone (as well as testosterone) can regulate NGF expression, in neurons and astrocytes [89, 90]. This hormone can also inhibit the production of CDF/LIF by heart cells and non-neuronal cells of sympathetic ganglia [91-92]. This regulation can alter the phenotype of neurons cultured with such non-neuronal cells.

Another aspect of cytokine action in the adult nervous system is the response to injury. Wounds in the CNS or interruption of a peripheral nerve results in the upregulation of many growth and differentiation factors, including CDF/LIF, NGF, TGF-β1 and glial maturation factor β [1, 76, 93-95]. Tumor necrosis factor α (TNFα), IL-1α, FGF and epidermal growth factor (EGF) have similarly been implicated in the response to nerve injury [94, 96-102]. Although the interplay of these signaling agents with neurons, glia and immune cells is not well understood as yet, damaged neurons may participate in feedback loops involving trophic and differentiation factors. For example, transecting postganglionic nerves or culturing sympathetic ganglia for 24 h induces the neuropeptides vasoactive intestinal polypeptide (VIP), SP and galanin (GAL) [103-106; M. Rao, J. L. Escary, Y. Sun, J. Perreau, P. H. Patterson, R. E. Zigmond, P. Brulet, and S. C. Landis, submitted]. It is notable that the neuropoietic cytokines can induce the same neuropeptides in sympathetic neurons. Moreover, transection of these nerves or culturing the ganglia evokes an enormous rise in CDF/LIF mRNA [76]. Linking these observations is the recent finding that sympathetic ganglia from CDF/LIF-deficient mice do not display this striking increase in VIP and GAL expression upon explantation to culture or axotomy (M. Rao, J. L. Escary, Y. Sun, J. Perreau, P. H. Patterson, R. E. Zigmond, P. Brulet, and S. C. Landis, submitted). Thus, CDF/LIF mediates a major part of the neuropeptide induction that occurs in response to injury.

Why is neuropeptide phenotype altered when sympathetic neurons are damaged ? One possibility is that the neuropeptides play a trophic role. Tissue injury and inflammation, for instance, alter neuronal gene expression through enhanced nociceptor activity, and the induced neuropeptides and excitatory amino acids are thought to be involved in the axonal sprouting and plasticity associated with these injuries, and with nerve damage [107, 108]. Another possibility is that the neuropeptides can act on immune cells. A SP antagonist can act as a potent inhibitor of neurogenic inflammation [109]. In the case of sympathetic neurons, it may be important to alter the neuropeptides the neurons are producing. Local release of CDF/LIF would induce sympathetic neurons to produce neuropeptides known to attract and activate immune cells (VIP and SP) [110, 111]. There is evidence that sympathetic axons participate in the inflammation associated with arthritis [112]. A role for CDF/LIF in the nervous system injury response fits nicely with its proposed functions in the hematopoietic and hepatic responses to infection [113].

Synaptic plasticity

A major feature of the issues considered thus far is that dynamic alterations in transmitter/neuropeptide expression can occur in mature neurons. This response can be a result of normal fluctuations in neuronal activity or hormone levels, or in response to injury. These changes in neuronal gene expression can entail qualitative changes in the mode of synaptic transmission (e.g. chemical switching), and are

likely to influence the behaviors associated with the estrous cycle, for instance.

Alterations in synaptic transmission are also believed to be central to the complex events comprising learning and memory. Long-term potentiation (LTP) of synaptic efficacy is one of the most intensively studied mechanisms in this regard [114]. Are cytokines involved in LTP and similar types of synaptic plasticity ? Clearly, neurotrophin expression can be regulated by neuronal activity on a time scale of hours [70, 115-118]. Moreover, a stimulus paradigm used to induce LTP in hippocampal slices increases BDNF and NT-3 mRNAs [119]. Stimulation of intact neocortex releases heat-labile factors that enhance neurite outgrowth from PC12 cells and induce LTP in slices of hippocampus [120]. The LTP-inducing activities in the cortical superfusate are heterogeneous in size, ranging from <3 to >50 kD [121]. The high molecular weight fraction induces LTP soon after its application, while the smaller fractions require 50 min to induce potentiation. These results suggest that diverse molecules and mechanisms are involved.

Known cytokines and their antagonists are also being tested in LTP assays. In hippocampal slices, EGF and FGF enhance potentiation of the population spike amplitude and field excitatory postsynaptic potential slope in the CA1 region [122, 123]. These effects are observed at 6-60 ng/ml of cytokine [124]. The action of the two cytokines is distinct ; enhancement of LTP by EGF is greater in the earlier phase, while the effect of FGF is greater in the later phase [123, 124]. These time periods correspond to the induction and maintenance phases of LTP. Cytokine administration can also be effective in the living animal. EGF and FGF, but not NGF, increase the magnitude and probability of LTP induction in the dentate gyrus of the intact hippocampus [125]. The mechanism of LTP facilitation by EGF is being pursued in dissociated hippocampal neurons. Using the fura-2 assay, EGF and bFGF are found to significantly enhance the intracellular calcium increase induced by N-methyl-D-aspartate (NMDA; a glutamate analog) [126, 127]. These results suggest that both proteins selectively enhance NMDA receptor-mediated responses in hippocampal neurons, an effect that could contribute to the facilitation of LTP by these cytokines.

In contrast to the effects of EGF and FGF, IL-1β induces synaptic inhibition in rat hippocampal pyramidal neurons [128]. This result could be due to the inhibitory function of SOM, which can be induced by IL-1β in the cortex [129]. Interferon and IL-2 can suppress previously established LTP as well as its induction in the hippocampus [130, 131]. TNF-α can affect LTP an hour after its addition to hippocampal slices [132].

The relatively rapid effects of the cytokines in these assays raise the question of whether they can influence intercellular signaling directly, rather than through the alteration of gene expression. Many cytokine receptors have tyrosine kinase domains [133], and electrophysiological and genetic evidence implicate protein kinases in LTP [134-136]. Thus, cytokines could indeed act directly as neuromodulators or neurotransmitters.

It is also possible that cytokine-driven changes in gene expression may be involved in learning and memory. Long-term changes in synaptic efficacy involve RNA and protein synthesis, and there is evidence that some aspects of LTP may also require new protein synthesis [137]. In fact, cytokines can induce major changes in neuropeptide expression rather quickly; 20-fold increases in SP and VIP mRNAs were observed in sympathetic ganglia within 24 h [138]. Thus, the instructive actions of cytokines could be involved in relatively short-term synaptic plasticity, as well as in the consolidation phase of memory or its conversion from short- to long-term storage. An intriguing correlation in this respect is the recent finding that one of the genes induced in the hippocampal dentate gyrus by the glutamate analog kainate is MyD118, a gene that is also induced by CDF/LIF and IL-6 in myeloid cells [139]. If nothing else, this finding suggests common signaling pathways for cytokine action and activity involved in long term plasticity.

Another point at which cytokines could influence learning is in the morphological changes that can accompany learning and related behavioral paradigms. It is now clear that anatomical connections are continually remodeled in adult as well as developing nervous systems, and some of these changes can be linked directly to learning [53, 140-144]. A particularly intriguing example in this context are the structural changes that accompany long-term synaptic facilitation in *Aplysia*. In this case, growth of presynaptic processes requires the presence of the postsynaptic neuron, suggesting the action of a retrogradely acting trophic factor [145-147]. Once more, the suggestion is that the same developmental mechanisms employed to set up the wiring system can be used in the mature brain to modify these connections [148].

Perspectives

It is clear that cytokines can act as neuronal trophic and differentiation factors, and that these agents are probably utilized in both the retrograde and anterograde directions. There are newly emerging families of cytokines and receptors that, along with other superfamilies, are involved in 1) the response to injury, and the feedback between the immune and nervous systems, 2) the ongoing functions of the organism, 3) the changes in synaptic plasticity involved in learning and memory, and 4) possibly in synaptic transmission directly. The ability to regulate neuropeptide expression, both quantitatively and qualitatively, adds another dimension to the plasticity and capacity for change that is becoming clear from experimental manipulations of the CNS. This regulation can dramatically alter synaptic function, both rapidly, in short-term physiological assays, or over the course of a day or month. These changes in synaptic function appear to contribute in key ways to complex animal behaviors, such as estrous, the stress response, and possibly circadian rhythms. While evidence is accumulating that cytokines may be involved in experimental paradigms of learning and memory, it is not yet clear if this involvement is in the context of neurotransmitter/neuropeptide regulation, physical rearrangement of synaptic contacts, or through direct action on membrane tyrosine kinases and signal cascades. Another frontier is the potential use of cytokines in the treatment of pathological conditions in the

nervous system. Clinical trials are underway to test the efficacy of these agents in the neurotrophic context where neurons are dying, but they could also prove useful in the manipulation of transmitter/neuropeptide imbalances in mental disorders. Moreover, genetic testing for predisposition to particular conditions could open the way for early, prophylactic intervention with these factors. ▼

Acknowledgments : I thank Floreen Rooks-Les Pierre for help in preparing the manuscript, and Herman Govan and Ming-ji Fann for their helpful comments on the text.

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